PHARMACEUTICAL COMPOSITION TO CONTROL BLOOD GLUCOSE IN PATIENTS WITH TYPE 2 DIABETES

Field of the Invention

[0001] This invention consists of providing a therapeutic combination consisting of the sulfonylurea glimepiride and the biguanide metformin, both oral hypoglycemics, which, when combined, produce not only an additive effect but also a synergistic effect and therefore greater effectiveness in controlling blood glucose levels in patients with type 2 diabetes.

BACKGROUND

[0002] The use of sulfonylureas in treating type 2 diabetes is fully established as an effective means of controlling hypoglycemia. At the molecular level, sulfonylureas act on the receptor in β pancreatic cells known as SUR, which, when it is activated, closes an ATP dependent potassium channel, which in turn causes a reduction in potassium intake and in consequence depolarization of the membrane. This in turn causes an increase in the flow of calcium toward the cell's interior, activating the cytoskeleton, which causes translocation of secretory granules, thereby releasing insulin by exocytosis.

[0003] Another treatment whose use has spread recently is with the biguanide metformin, which acts effectively not only to control hypoglycemia, but also in its prevention. Metformin has a different mechanism of action from sulfonylureas, increasing insulin sensitivity in hepatic and peripheral tissue (mainly muscular tissues). Metformin inhibits gluconeogenesis and hepatic glycogenolysis. At the cellular level, heightened insulin sensitivity is explained by the increased activity it induces in the tyrosin kinase post-receptor and the resulting increase in the number and activity of GLUT4 transporters.

[0004] However, around 75% of type 2 diabetes patients treated with sulfonylureas do not succeed in bringing their glucose level to the desired values, and need to complement their treatment with a second oral agent. Also, most patients with single drug treatment using sulfonylureas after a certain number of years require an additional drug that contributes to their

control therapy in order to achieve a suitable level of glycemic control. This loss of effectiveness is attributed to various causes, which are not yet well established, such as the supposition that gradual deterioration of the pancreas renders it unable to maintain an exacerbated insulin excretion rate for a long period of time due to constant, long-term stimulation caused by sulfonylurea therapy. However, contrary to this explanation, metformin therapy, which does not act by over stimulating β cells, also presents lack of response after prolonged use, which would be contradictory to the explanation given for the lack of response of sulfonylureas.

[0005] On the other hand it has been found that combining sulfonylurea and metformin therapy is more effective than monotherapy with either of the two medications. Thus, it has been fully proven that the hypoglycemic action of metformin is completely additional to that of sulfonylureas (de Fronzo, R.A. and Goodman, A.M. Yn, *England J. Med. 333*:541 (1995)).

[0006] Its also has been reported that when monotherapy with sulfonylureas does not achieve the desired levels it should not be discontinued and replaced by metformin monotherapy, as this will not lower glucose levels in plasma below the values observed with sulfonylurea monotherapy (Rosenstock, J. *et al., Diabetes Care* 19:1994 (1996); (Gasber, A.J., *et al., Amer. J. Med.* 103:491 (1997)).

[0007] It is generally recognized that, because diabetes mellitus is a progressive disease, patients with good initial response to oral agents will eventually require a second medication to achieve the desired glycemic control. As we have mentioned, adding metformin to sulfonylurea therapy or vice-versa produces an additive response, not only to the reduction in glucose, but also to the reduction in lipids (Hermann, L.S., *et al., Diabetes Care,* 17:1100 (1994)).

[0008] There are several reports on the combined use of the sulfonylurea glibenclamide with the biguanide metformin. See, e.g., WO 97/17975; Vigneri *et al., Diabetes and Metabolism*, 17:232-234 (1991); Higginbotham *et al., Med.J.Austr.*, 154-156 (1979); U.S. Patent No. 6,303,146; and WO 01/32,158.

[0009] Furthermore, there are several references on the combined use of the sulfonylurea glipizide with metformin. See, e.g., Cefalu *et al.*, *Diabetes*, 45 (Supl. 2):201A (1996); Croase *et al.*, *Circulation*, 94 Supl 1508 (1996); and Cefalu *et al., Diabetology*, 39 (Supl. 1): A231 (1996).

[0010] It has been reported that there are no great differences in efficacy among various sulfonylureas (R.A. De Fronzo, *Annals of Internal Medicine*, 131:281-303 (1999)); S. Dagogo-Jack, *et al.*, *Archives Internal Medicine*, 157:1802-1817 (1997); A.J. Scheen *et al.*, *Drugs* 55:225-236 (1998); R. Bressler *et al.*, *Archives Internal Medicine*, 157:836-848 (1997). Other reports indicate that glimepiride shows a potency two times higher than that of glibenclamide (R. Groomis *et al.*, *Endocrinology*, 13:117-121 (2000)). Moreover, in contrast to glibenclamide, chronic treatment of type 2 diabetic patients with glimepiride will not impair the vasodilator function of K_{ATP} opening *in vivo* (E.J. Abbink *et al.*, *Diabetic Medicine*, 19:136-143 (2002). Furthermore, a lower incidence of severe hypoglycemia was reported in type 2 diabetic patients treated with glimepiride versus glibenclamide (A. Holstein *et al. Diabetologia*, 157:A40 (2000). Finally, Kramer *et al.*, *Biochimica et Biphysica Acta* 1191:276-290 (1999)), reported that glimepiride acts on a different receptor site on the β-cell than does glibenclamide, and that glimepiride interacts with the β-cell receptor for less time. Unlike glibenclamide, glimepiride seems to work in part by enhancing both the sensitivity and reponsiveness of peripheral tissue to insuline (J. Sato *et al. Excerpta Medica*, 341-348 (1994), G.E. Sonnenberg *et al.*, *Annales Pharmaceuticals*, 31:671-676 (1997)).

DESCRIPTION OF THE INVENTION

[0011] Combined glimepiride and metformin have been suggested previously in the literature (G. Charpentier *et al. Diabetic Medicine* 18:828-834 (2001)). However, very little data is provided on its advantages or appropriate dosages. The prescribing information for the drug Amaryl (which active ingredient is glimepiride) warns of its supposed risk of hypoglycemia due to concomitant

use metformin (Physicians Desk Reference, 54 Edition, 2000, page 1349). Thus, the current state of the art does not suggest the development and use of a pharmaceutical composition combining glimepiride and metformin, which in the present invention has been found to offer unexpected advantages.

[0012] With the present invention we have performed clinical studies which indicate that a pharmaceutical composition comprising a combination of glimepiride and metformin in determined fixed ratios decreased the glycosylated haemoglobin (HbA_{1c}) in a synergistic way compared to using glimepiride and metformin separately (Gonzalez-Ortiz *et al.*, *Rev. Inv. Clin.* 56, in press, 2004). That is, the combined use of both drugs in certain ratios displays a synergistic effect on the efficacy greater than the additive efficacy of glimepiride and metformin used separately. This synergistic effect, beside being manifested in the control of glycosylated haemoglobin (HbA_{1c}), also controls fasting blood glucose (FBG) and post-prandial blood glucose (PPBG).

[0013] WO 00/40233 describes a pharmaceutical composition of glimepiride and metformin. However, this composition is designed to deliver an initial concentration of glimepiride, and later a delayed delivery of metformin. By this way of delivering both components it is not possible to maintain an appropriate bioavailability of the combined use of glimepiride and metformin to achieve a synergistic effect.

[0014] In the clinical studies performed concerning the present invention, it has been found that in order to obtain a pharmaceutical synergy, the ratio between metformin/glimepiride must be maintained in the range between about 500/1 to about 500/2 and using the appropriate dosage of metformin/glimepiride of 500/1, 500/2, 1000/2, 1000/4 (mg/mg), preferably 1000/2 mg/mg using a single dosage in a single tablet containing both drugs with 250 ml of water. After 10 hr of fasting in 16 healthy volunteers, 8 men and 8 women, the plasma concentrations of glimepiride was C_{max} = 194.43 +/- 63.51 ng/ml and for metformin 2245.16 +/- 580.91 ng/ml in a time of 1.98 +/1-0.59 hrs and 1.56 +/- 0.56 hrs, respectively. The half life of glimepiride was 3.73 +/- 1.28 hours, and of metformin was 2.62 +/- 0.33 hours. Using these conditions and the mentioned ratio of glimepiride and metformin a

synergistic control was observed in the glycosylated hemoglobin (HbA_{1c}), in the control of fasting blood glucose (FBG), and in the post-prandial blood glucose (PPBG).

[0015] The great inconvenience of the pharmaceutical composition described in the above mentioned patent WO 00/40233 A is that there is an initial and total delivery of glimepiride followed by a delayed delivery of metformin. Taking into account the short half life of glimepiride (around 3.73 hours), when the metformin starts delivering the glimepiride concentration in the blood will be falling such that there will be a variable proportion of both drugs in the blood as a function of time. After a longer period of time, the glimepiride will be cleared from the blood and only the delayed metformin will persist. The net effect is a sequential medication of glimepiride alone followed by a combined medication of glimepiride and metformin with variable concentrations in the blood, followed by the supply of metformin alone. With this type of bioavailability, it will be impossible to observe any synergistic effect of the combination of both drugs.

[0016] The purpose of this invention is to provide a pharmaceutical composition consisting of glimepiride and metformin as its hydrocloride salt, or any other salt, and oral hypoglycemic therapy combining glimepiride and metformin in a single fixed ratio that is more effective and just as safe as monotherapy with the same compounds in patients with uncontrolled type 2 diabetes mellitus.

[0017] To demonstrate the above, a random double blind clinical study was conducted with a universe of 30 patients with uncontrolled type 2 diabetes mellitus who receive monotherapy with sulfonylureas or biguanides per group.

[0018] Criteria for inclusion were as follows:

1. Body mass index = 27 kg/m^2;
2. Age 40 to 65;
3. Capacity for deglutition; and
4 Voluntary consent

[0019] Criteria for exclusion were as follows:

1. Pregnancy;

2. Insulin treatment; and

3. Personal background of systemic diseases such as:

a) Cardiac insufficiency; and

b) Hepatic or chronic hepatopathic insufficiency.

4 Background of significant chronic complications with type 2 diabetes mellitus:

a) Renal insufficiency;

b) Ischemic cardiopathy;

c) Cerebral vascular disease; and

d) Visceral neuropathy.

5. Background of short-term terminal diseases, such as:

a) Cancer; and

b) HIV

6. Therapy with medications that present pharmacological interaction with glimepiride or metformin, such as acetozolamide, nicotinic acid, para-aminosalicylic acid, non-steroidal anti-inflammatory analgesics, histamine antagonists 2, barbiturates, cyclophosamide, clonidine, cloranphenicol, cumarinics, disopyramide, epinephrine, estatines, fenfluramine, phenotiacine, fibrates, fluoxetine, guanitidine, steroid hormones, iphosamide, monoaminoxidase inhibitors, laxatives, miconazole, quinolones, reserpine, rifamicine, sulfamides, and tetracycline.

7. Known intolerance or allergies to sulfonylureas or biguanides.

[0020] Criteria for exclusion from the therapy, but not from the statistical analysis:

1. Presence of severe hypoglycemia at the maximum dosages used in the study;

2. Presence of severe hypoglycemia at the minimum dosages used in the study;

3. Presence of intolerable undesirable effects with any of the medications used in the study;

4. Failure to follow the medical treatment indicated.;

5. Failure to attend scheduled visits;

6. Intercurrent illnesses or accidents that warrant hospitalization;

7. Administration during the study of medications with pharmacological interaction with metformin or glimepiride; and

8. Voluntary withdrawal from the study.

[0021] The variables studied were as follows:

Dependent variables:

a) Glycemia between meals;

b) Glucosylated hemoglobin;

c) β cell function;

d) Insulin resistance; and

e) Metabolic profile.

Independent variable:

a) Hypoglycemic therapy.

Intervening variables:

a) Age;

b) Sex;

c) Body mass index; and

d) Evolution of diabetes.

Definitions

[0022] Levels of glycemia between meals > 139 mg/dL are defined as type 2 diabetes mellitus.

[0023] Severe hypoglycemia: Glycemia between meals > 260 mg/dL.

[0024] Severe hypoglycemia: Glycemia < 60 mg/dL.

[0025] Non-adherence: Medication absorption <80%.

[0026] Absence: Missed appointment on > 1 occasion.

Procedure

[0027] Identification, clinical history and selection of participants:

[0028] Clinical measurements and basal measurement of glycemia between meals, glucosylated hemoglobin, total cholesterol, cholesterol of high density lipoproteins, triglycerides, creatinine, uric acid, glutemic-oxaloacetic

transaminase, glutemic-pyruvic transaminase, lactic dehydrogenase, alkaline and insulin phosphatase.

[0029] Random assignment of patients to each group and pharmacological intervention in accordance with concentration of basal glycemia:

a) Glimepiride (2 mg tablets)

Glycemia 140-180 mg/dl	1 mg	½ tablet
Glycemia 181-220 mg/dl	2 mg	1 tablet
Glycemia 221-260 mg/dl	4 mg	2 tablets

b) Metformin (1000 mg tablets)

Glycemia 140-180 mg/dl	500 mg	½ tablet
Glycemia 181-220 mg/dl	1000 mg	1 tablet
Glycemia 221-260 mg/dl	2000 mg	2 tablets

c) Glimepiride/Metformin (2/1000 mg tablets)

140-180 mg/dl	1/500 mg	½ tablet

[0030] Clinical evaluation 30 and 60 days after beginning the study, measuring glycemia between meals and lactic dehydroginase.

[0031] Final clinical evaluations 90 days after the study begins, measuring glycemia between meals, glucosylated hemoglobin, total cholesterol, high density lipoprotein cholesterol, triglyceride, creatinine, uric acid, glutemic-oxaloacetic transaminase, glutemic-pyruvic transaminase, lactic dehydrogenase, alkaline and insulin phosphatase.

[0032] Undesirable effects were reported on a special record sheet, specifying each of the clinical manifestations considered probable, possible or directly related to the use of the drugs ingested.

[0033] The results obtained show that combined metformin and glimepiride therapy was more effective in controlling glucosylated hemoglobin levels, post-prandial blood glucose levels and blood glucose levels between meals

than single-drug treatment with glimepiride or metformin alone. The results obtained are shown below:

	Combination	glimepiride	metformin
Glucosylated hemoglobin HbA_{1c}	-0.70	+0.25	+0.06
Blood glucose between meals	-1.77	+0.68	+0.75
Post-prandial blood glucose	-2.7	+0.99	+1.08

[0034] What is extraordinary about the values obtained is that monotherapy with either glimepiride or metformin has a similar effect in raising glucose levels, while treatment with the combination clearly shows a beneficial effect, which highlights its importance.

[0035] The previous combinations used in the clinical study can be illustrated by means of the following examples:

Example 1

[0036] A pharmaceutical composition is prepared consisting of 500 mg of metformin hydrochloride and 1 mg of glimepiride, adding the following excipients:

Microcrystalline Cellulose PH 101	39.20 mg
Coloidal Silica Dioxide	1.80 mg
Povidone K-90	18.00 mg
Croscarmelose Sodium	12.00 mg
Magnesium stereate	3.00 mg
Clear Opadray YS-1-7006	5.00 mg
Purified water	0.204 mg

[0037] This pharmaceutical composition was used for the aforementioned clinical tests.

Example 2

[0038] A pharmaceutical composition is prepared consisting of 500 mg of metformin hydrochloride and 2 mg of glimepiride, adding the following excipients:

Microcrystalline Cellulose PH 101	38.20 mg
Coloidal Silica Dioxide	1.80 mg
Povidone K-90	18.00 mg
Croscarmelose Sodium	12.00 mg
Magnesium stereate	3.00 mg
Clear Opadray YS- 1 -7006	5.00 mg
Purified water	0.204 mg

[0039] This pharmaceutical composition was used for the aforementioned clinical tests.

Example 3

[0040] A pharmaceutical composition is prepared consisting of 1000 mg of metformin hydrochloride and 2 mg of glimepiride, adding the following excipients:

Microcrystalline Cellulose PH 101	78.40 mg
Coloidal Silica Dioxide	3.60 mg
Povidone K-90	36.00 mg
Croscarmelose Sodium	24.00 mg
Magnesium stereate	6.00 mg
Clear Opadray YS-1-7006	6.25 mg
Purified water	0.345 ml

[0041] This pharmaceutical composition was used for the aforementioned clinical tests.

Example 4

[0042] A pharmaceutical composition is prepared consisting of 1000 mg of metformin hydrochloride and 4 mg of glimepiride, adding the following excipients:

Microcrystalline Cellulose PH 101	78.40 mg
Coloidal Silica Dioxide	3.60 mg
Povidone K-90	36.00 mg
Croscarmelose Sodium	24.00 mg
Magnesium stereate	6.00 mg
Clear Opadray YS-1-7006	6.25 mg
Purified water	0.345 ml

[0043] This pharmaceutical composition was used for the aforementioned clinical tests.